29. (New) A method according to claim 10, wherein the antibody is a chimeric antibody.

REMARKS

Claims 10-20 are pending. Claims 10, 15, 16 and 18 have been amended. Claims 11 and 19-20 have been canceled. New claims 25-29 have been added. No new matter has been added.

Claims 10-19 have been rejected under 35 USC § 112, first paragraph. Claims 10-19 have been rejected under 35 USC § 112, second paragraph. Claims 10, 11, 15-17 and 20 have been rejected for double patenting. Claim 20 has been rejected under 35 USC § 102(b).

The rejections are addressed below in the order they appear in the Office Action.

Restriction Requirement

Applicant affirms the election to prosecute the invention of Group II, claims 10-20, and species 2, claims 12-14.

Formalities

A new declaration under 37 CFR §1.67(a) will be provided upon indication of allowable subject matter.

The objection regarding incorporation by reference of the subject matter of USSN 08/376,372 is respectfully traversed. Nothing disclosed in USSN 08/376,372 is essential for the practice of the claimed invention.

Correction of Figure 5 will be provided upon indication of allowable subject matter.

35 USC § 112, first paragraph

Claim 11 was rejected under 35 USC § 112, first paragraph, as failing to provide adequate written description of the invention and failing to provide an enabling disclosure.

The Examiner states (at pages 6-9):

> The claim is drawn to monoclonal antibody HP1/2 and fragments thereof used in a method of treating diabetes.

It is unclear if a cell line which produced an antibody having the exact structural and chemical identity of HP1/2 is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing monoclonal antibody HP1/2, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of the ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, HP1/2. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the antibody species, HP1/2. If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. where it is desired to rely on an earlier filed affidavit, the applicant should make remarks of record in the later application and include a copy of the original affidavit filed in the parent application.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

The rejection is met by canceling claim 11.

Claims 10, 11, and 15-18 were rejected under 35 USC § 112, first paragraph.

The Examiner states (at page 9):

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant invention commensurate with the scope of the claims. The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The specification provides no guidance on or exemplification of how to use the claimed immunotherapeutic method for successful treatment of any diabetes other than type I diabetes in NOD mice.

This part of the rejection is met by amending claim 10. As amended, the claim is directed to a method of treating insulin dependent type I diabetes.

The Examiner states (at pages 9-10):

Further, the specification discloses data based solely on an adoptive diabetes transfer experiment in NOD mice. The spleen cells which were transferred to the NOD mice were treated with the R1-2 mAb

which is an antibody specific for VLA4. The antibody was then administered to the transfer model for two weeks in order to coat the VLA4 positive cells. In general, data such as that disclosed in the specification, cannot be extrapolated to predict human efficacy *in vivo* as it would be impossible to duplicate the saturation of spleen cells with the desired antibodies prior to onset of the disease. It would appear that although the NOD model is effective in studying the onset of diabetes, it is not sufficiently correlative of therapeutic utility. Further, the art does not recognize a reliable correlation between mouse animal model data such as those presented in the specification and human efficacy.

This part of the rejection is respectfully traversed. NOD mice are an art recognized animal model for human type I diabetes. Many key features of human type I diabetes are reflected in NOD mice: (1) the development of insulitis; (2) the inheritance of particular major histocompatibility complex (MHC) class II alleles, representing the major component of genetic susceptibility; (3) the transmission of diabetes by hematopoietic cells in bone marrow; and (4) the T cell dependence of the disease pathogenesis. Table 1 below sets out these and other paralleles between the human disorder and NOD. The table is reproduced from Bowman et al. *Immunology Today* 15(3):115-120, 1994, a copy of which is enclosed.

Table 1. Comparison of insulin-dependent diabetes in humans and NOD mice

Characteristic	Humans	NOD mice
Genetic predisposition (MHC class II linkage)	+	+
Complex polygenic control	+	+
Environmental effects on gene penetrance	Probable	+
Disease transmissible via bone marrow	+	+
T-lymphocyte-driven insulitic lesions	+	+
Leukocyte infiltrates found in other organs	Sometimes	+
Defective peripheral immunoregulation	+	+
Humoral reactivity to β cells	+	+
Endogenous retroviral genes expressed in β cells	-	+
Diabetic ketoacidosis if untreated	+	Mild
Gender Bias	±	+
Successful intervention therapies	Ongoing	+

The Bowman et al. reference further states (at page 19, last paragraph):

"The NOD mouse has provided a model system to study not only the pathogenesis and natural history of a disease that is similar to human IDD, but also a means with which to prevent the disease in humans." (emphasis added)

As outlined above, the NOD mouse model shares a number of important characteristics with human type I diabetes. The disease develops spontaneously and is not accompanied by general immunodeficiency as in some other animal models, e.g., the BB rat. Differences include simultaneous lymphocyte infiltration of salivary glands and other organs, and a strong female predominance. Despite these minor differences, study of mechanisms involved in insulitis, β-cell destruction, and the generation of other immunological disturbances allows hypotheses concerning human type I diabetes to be developed and tested (see, e.g., Lampeter et al., *Diabetologia* 32:703-708, 1989, a copy of which is enclosed).

Regarding the testing of new therapies the Pozzilli et al., *Immunology Today* 14(5):193-196, 1993 reference, a copy of which is enclosed, states (at page 196, last paragraph):

"All new therapies aimed at preventing Type 1 diabetes should first be tested on animal models of the disease and the NOD mouse is one of the most appropriate models for this purpose." (emphasis added)

The Examiner further states (at pages 10-11):

Osband et al. (Immuno. Today, 11:193-195, 1990) teach on pages 193-194 that while the response of animals to chemotherapy, radiation and surgery is generally predictive of their effect in human patients, this is not the case with immunotherapy. This is due in part, to the fact that animal models do not fully mimic the biology of human patients. Harris (Tibtech, 11:42-44, 1993) teaches that "there is widespread acceptance that there is little future for the use of rodent mAbs in human therapy." Harris does however, say that humanized antibodies show some potential, but is unwilling to definitively commit to this view until further "clinical" data has been presented and evaluated (see whole article). In view of the contemporary knowledge in the art of the general lack of successful application of monoclonal antibody-based therapy methods for treatment of human diseases and of the limited predictive value of animal results for efficacy in humans, as well as the lack of sufficient guidance in the specification,

one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

This portion of the rejection is respectfully traversed. Applicant has discovered that blocking the VLA4/VCAM-1 interaction results in delaying the onset of diabetes-like symptoms in NOD mice. Human type I diabetes is characterized by lymphocyte infiltration of the pancreas. Lymphocytes, which express VLA-4, are important agents of inflammatory related damage. There is no reason to believe that blocking the VLA-4/VCAM-1 interaction in humans would not produce results similar to those in NOD mice.

The application claims methods of treating insulin dependent type I diabetes by the administration of an anti-VLA-4 antibodies or soluble VCAM or fibronectin polypeptides. The application includes an example in which the administration of anti-VLA-4 antibody (R1-2) significantly inhibited onset of diabetes in a mammalian NOD mouse model. (See, e.g. pages 11:36-14-14 of the specification). The specification also discloses on page 21 that the adoptive transfer experiment described for the antibodies was repeated successfully with the soluble VCAM molecule, i.e., VCAM 2D-IgG. That Applicant's assertions in the specification were correct is shown in Yang et al., 1994, PNAS 91:12604-12608, a copy of which is enclosed, which discloses experiments in which diabetes-prone mice were administered rat anti-mouse VLA-4 antibodies twice weekly for 8 weeks. The onset of diabetes was significantly delayed. These experiments were not "adoptive transfer" experiments. Rather, rat mAb was directly administered to the subject NOD mice.

Harris states that there is little future for rodent monoclonal antibodies. Despite what Harris et al. may say, murine monoclonal antibodies have been shown to be therapeutically effective in a number of human settings. Examples of success with rodent antibodies are discussed below.

Hooks et al. (*Pharmacotherapy* 11(1):26-37, 1991), shows that Muromonab™ CD-3, an FDA approved commercial murine antibody (mAb OKT3), is highly efficacious for the *in vivo* treatment of human kidney graft rejection. Indeed on page 29, column 2, Hooks et al. states:

> "The use of OKT-3 in organ transplantation has increased due to its overwhelming success in reversing allograft rejection. The majority of studies conducted have been in patients undergoing renal transplantation, but promising results have also been demonstrated in liver and heart transplantation."

A recent meeting, "Monoclonal Antibodies and Cancer Therapy: The Next Decade", New York, October 16-18, 1995, focused on the use of monoclonal antibodies in human cancer therapy. The enclosed article *J. Nat. Cancer Inst.* 87(22):1658-1660 (1995)) discussed some of the content of the meeting. Note that on page 1659, five murine monoclonal antibodies (17-1A, anti-B1, IDEC-C2 (an anti-CD20 antibody), anti-Her2/ncu (directed against a breast cancer protein), and anti-B4-bR) have entered, or are about to enter, large randomized or multicenter trials. Applicant also notes that MAb 17-1A has been approved for human use in Germany.

Claims 10-14 and 16-17 were rejected under 35 USC § 112, first paragraph.

The Examiner states (at pages 11-12):

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant invention commensurate with the scope of the claims, The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The specification provides no guidance on or exemplification of how to use the claimed polypeptide therapeutic method for successful treatment of any diabetes other than type I diabetes in NOD mice. The specification states on Page 21 that the adoptive transfer experiment described for the antibodies was repeated successfully with the VCAM 2D-IgG. The specification does not address the pharmacokinetic properties of VLA4 binding peptides. At the time of filing of the instant application it was known that different proteins and peptides exhibited not only different clearance capabilities but different cross reactivities. Further, because *in vivo* administration of a polypeptide may involve different routes, dosages, schedules, etc., and also exposes the polypeptide to complex environments including blood cells and proteins, and also diverse organs such as the liver, lungs, kidney, and spleen, the fate and activity of the polypeptide is unpredictable regarding its ability to bind VLA-4 *in vivo* in and can't be predicted in humans because animal models do not fully mimic the biology of human patients.
>
> In view of the contemporary knowledge in the art of the limited predictive value of animal results for efficacy in humans, as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

The rejection is met by deleting "polypeptides and small molecules" from the claims.

Claims 10, 11, 16, 17 and 19 were rejected under 35 USC § 112, first paragraph.

The Examiner states (at pages 12-13):

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant invention commensurate with the scope of the claims. The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The specification provides no guidance on or exemplification of how to use the claimed small molecule therapeutic method for successful treatment of any diabetes. The specification defines small molecules as those that mimic the action of anti-VLA-4 antibodies in the treatment of diabetes (p. 4, lines 36-37) and carbohydrates (p. 4, line 15) but does not give guidance as to administration of a small molecule or which specific small molecules would mimic the action of anti-VLA-4 antibodies in the treatment of diabetes, further, the specification does not address the pharmacokinetic properties of VLA4 modulating small molecules. At the time of filing of the instant application it was known that small molecules exhibited not only different clearance capabilities but different cross reactivities. Further, because *in vivo* administration of small molecules may involve different routes, dosages, schedules, etc., and also exposes the small molecules to complex environments including blood cells and proteins, and also diverse organs such as the liver, lungs, kidney, and spleen, the fate and activity of the small molecules is unpredictable regarding their ability to mimic the action of anti-VLA-4 antibodies *in vivo*.
>
> In view of the unpredictability pertaining to the ability of small molecules to mimic the action of anti-VLA-4 antibodies *in vivo* as discussed above as well as the lack of sufficient guidance in the specification, on of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

The rejection is met by amending claims 10 and 16 and canceling claims 11 and 19. As amended, the claims no longer encompass small molecules.

Claims 10-19 were rejected under 35 USC § 112, first paragraph.

The Examiner states (at pages 13-14):

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant invention commensurate with the scope of the claims, The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans, The claims as drawn read on the treatment of diabetes on all stages of the disease. The specification provides no exemplification of how to use the claimed antibodies and polypeptides for the treatment of diabetes once damage has been done and the Islet cells are dead. The mechanism of action of treatment by the claimed antibodies and polypeptides is blockade of binding of VACM-1 to VLA-4 which prevents the adhesion of leukocytes to inflamed endothelium, protecting Islet cells from damage and cell death, thus the efficacy of the instant method for treatment of diabetes, when the Islet cells are already dead would be highly unpredictable.
>
> In view of the unpredictability pertaining to the efficacy of treating diabetes with the instant invention when the Islet cells are already dead as discussed above as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

The rejection is respectfully traversed. The claims are directed to delaying the onset of diabetes. It seems highly unlikely that all islet cells would already be dead in such individuals.

Claims 10-19 were rejected under 35 USC § 112, first paragraph.

The Examiner states (at pages 14-16):

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant invention commensurate with the scope of the claims. The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The claims as drawn read on an all antibodies, polypeptides and small molecules that bind to all VLA-4 positive cells. Jabukowski et al (J. Immunol, 1995, 155: 938-946) specifically teach that monoclonal antibodies R1-2 and PS/2 bind to all alpha 4 positive cells *in vitro* and *in vivo* infusion and reports a VCAM-Ig fusion polypeptide that is specific for activated receptors, preventing the binding of VLA-4 to inflamed tissues required for the inflammatory response, sparing the majority of circulating and tissue resident cells (p.

943, para 3). Further, Jabukowski et al teach that lymphocytes, monocytes, macrophages, eosinophils and basophils adhere to VCAM-1 through VLA-4 (p. 938). The specification gives no guidance or exemplification of how to use the claimed method of administering antibodies, polypeptides or small molecules to specifically target cells, in humans, involved with the inflammation related pathogenesis of diabetes. Treatment of diabetes with the administration of the claimed antibodies, polypeptides or small molecules that bind to all VLA-4 positive cells would perturb the complex regulatory network involving these cell types and eliminate binding of VLA-4 positive cells to VCAM-1 positive tissues. Elimination of suppressor T cell function would be expected to interfere with suppressor T cell functions, for example, the inhibition of cytotoxic T cells that mediate the pathogenesis of diabetes. Thus, the effects of the treatment by the instant method would be highly unpredictable and could exacerbate rather than treat, diabetes.

In view of the unpredictability pertaining to the effects of treatment by the instant method as discussed above as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

The portion of the rejection directed to the use of "polypeptides and small molecules" has been met by amending the claims so that they do not claim the use of these molecules. The balance of the rejection is respectfully traversed. The methods of the invention were shown to treat and not exacerbate the diabetes-like condition in NOD mice.

35 USC § 112, second paragraph

Claims 10-19 were rejected under 35 USC § 112, second paragraph, as being indefinite to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states (at pages 16-17):

Claims 10-19 are indefinite because claim 10 recites an improper Markush group. MPEP 706.03(y) provides that the materials set forth in a Markush group ordinarily must belong to a recognized physical class or chemical class or to an art-recognized class. When the Markush group occurs in a claim reciting a process or a combination it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is responsible for their function in the

claimed relationship and it is clear from their very nature or from the prior art that all of them possess this property.

The members of the Markush groups recited in claim 10 do not belong to a recognized class nor do they function by a common mechanism to treat or prevent diabetes. The Markush groups of claim 1 recite antibodies which are immunoreactive with the gamma 4 subunit of VLA-4 which act by complexing with the gamma 4 subunit of VLA-4 to prevent complex formation and the polypeptide acts by competing with endogenous polypeptides or small molecules to prevent complex formation. The above embodiments should be set out as separate claims. The mechanism of action of a small molecule is unclear because of the indefinite language used.

Claim 10-19 are indefinite for because claim 10 is in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

Claims 10-19 are indefinite because claim 1 recites the phrase "or small molecule". It is not clear what is meant by a small molecule, for example, is it a protein, a peptide, Calcium, or magnesium?

Claims 10-19 are indefinite because claim 1 recites the phrase "or combinations of any of the foregoing". It is not clear which or how many combinations of antibodies, polypeptides or small molecules are claimed for patent protection.

The rejection is met by amending claims 10 and 16 and canceling claims 11 and 19. As amended, the claims use a proper Markush format suggested by the Examiner and the members of the Markush group all function by binding to the α4 subunit of VLA4. As amended, the claims no longer encompass "a polypeptide or a small molecule."

The Examiner further states (at pages 17-18):

Claim 11 is indefinite because claim it recites an improper Markush group. The members of the Markush groups recited in claim 11 do not belong to a recognized class nor do they function by a common mechanism to treat or prevent diabetes. The Markush groups of claim 11 recite antibodies which are immunoreactive with the gamma 4 subunit of VLA-4 which act by complexing with the gamma 4 subunit of VLA-4 to prevent complex formation and the VCAM-1 or fibronectin polypeptides act by competing with endogenous VACM-1 or fibronectin polypeptides to complex formation. The above embodiments should be set out as separate claims. The mechanism of action of a small molecule is unclear because of the indefinite language used.

Claim 11 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03 (Y).

Claim 11 is indefinite because it recites the phrase "or small molecules". It is not clear what is meant by small molecules, for example, are they proteins, a peptides, Calcium, or magnesium?

Claim 11 is indefinite because it recites the phrase "small molecules". It is not clear whether one small molecule or many small molecules bind to the VCAM-1 or fibronectin binding domain of VLA-4.

The rejection is met by canceling claim 11.

The Examiner further states (at page 18):

Claim 15 is indefinite because it recites the phrase "a plurality of ...monoclonal antibodies". It is not clear if it is one antibody or a group of different antibodies that are binding to VLA-4.

The rejection is met by amending claim 15.

The Examiner further states (at pages 18-19):

Claim 16 is indefinite because claim it recites an improper Markush group. The members of the Markush groups recited in claim 16 do not belong to a recognized class nor do they function by a common mechanism to treat or prevent diabetes. The Markush groups of claim 11 recite antibodies which are immunoreactive with the gamma 4 subunit of VLA-4 which act by complexing with the gamma 4 subunit of VLA-4 to prevent complex formation and the VCAM-1 or fibronectin polypeptides act by competing with endogenous VCAM-1 or fibronectin polypeptides to complex formation. The above embodiments should be set out as separate claims. The mechanism of action of a small molecule is unclear because of the indefinite language used.

Claim 16 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

Claim 16 is indefinite because it is unclear whether the compositions to be administered, that is antibody, polypeptide or small molecule, are to be administered separately or in combination.

The rejection is met by amending claims 10 and 16 and canceling claim 11. As amended claim 16 is limited to antibodies or fragments thereof.

The Examiner further states (at pages 19-20):

> Claim 17 is indefinite because claim it recites an improper Markush group. The members of the Markush groups recited in claim 17 do not belong to a recognized class nor do they function by a common mechanism to treat or prevent diabetes. The Markush groups of claim 11 recite antibodies which are immunoreactive with the gamma 4 subunit of VLA-4 which act by complexing with the gamma 4 subunit of VLA-4 to prevent complex formation and the VCAM-1 or fibronectin polypeptides act by competing with endogenous VCAM-1 or fibronectin polypeptides to complex formation. The above embodiments should be set out as separate claims. The mechanism of action of a small molecule is unclear because of the indefinite language used.
>
> Claim 17 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).
>
> Claim 17 is indefinite because it is unclear whether the compositions to be administered, that is antibody, polypeptide or small molecule, are to be administered separately or in combination.

The rejection is met by amending claim 10 and canceling claim 11.

The Examiner further states (at page 20):

> Claim 18 is indefinite because the word "fragment" is misspelled.
>
> Claim 18 is indefinite because it recites the phrase "period of 1-14 days". It is not clear it 2, 3, 6, or 12 days are being claimed for patent protection.

The portion of the rejection concerning the term fragment is met by amending claim 18. With respect to indefiniteness of the phrase "period of 1-14 days," the rejection is respectfully traversed. One of ordinary skill in the art would know this gives a range of time periods, e.g., 1 day, 5 days, or 14 days, during which the plasma level is maintained.

The Examiner further states (at page 20):

Claim 19 is indefinite because it recites the phrase "small molecule". It is not clear what is meant by a small molecule, for example, is it a protein, a peptide, Calcium, or magnesium?

Claim 19 is indefinite because it recites the phrase "period of 1-14 days". It is not clear if 2, 3, 6, or 12 days are being claimed for patent protection.

The rejection is met by canceling claim 19.

Claim 20 is indefinite because it recites the phrase "consisting essentially of". The specification does not define the phrase. Does "consisting essentially of" include polyclonal antibodies, polypeptides and small molecules? Rejection of the claim can be obviated by amending the claim to delete the phrase "consisting essentially of" and replacing it with "comprising".

This rejection is met by canceling claim 20.

Double Patenting

Claims 10, 11, 15-17 and 20 have been provisionally rejected under 35 USC §101 as claiming the same invention as that of claims 10-11, 12-14 and 16 of copending application Serial No 08/447,098. This provisional rejection will be met when claims have been allowed in both applications. Claims 11 and 20 have been canceled.

Claim 18 has been provisionally rejected for obviousness-double patenting as being unpatentable over claim 13 of copending application Serial No 08/447,098. This provisional rejection will be met when claims have been allowed in both applications.

Claim 19 has been provisionally rejected for obviousness-double patenting as being unpatentable over claim 14 of copending application Serial No 08/447,098. Claim 19 has been canceled.

35 USC § 102

Claim 20 was rejected under 35 USC § 102(b) as being anticipated by Elices et al. or Issekutz.

The Examiner states (at pages 22-23):

The claim is drawn to a pharmaceutical composition comprising an antibody which recognized VLA4, wherein the composition is in a

pharmaceutically acceptable carrier and is able to prevent the onset of diabetes. first it should be noted that the intended use clause in the claim has no patentable weight on the examination of the product which in this case is an anti-VLA4 antibody. Second, in general, any buffer which contains the monoclonal antibody, e.g. water or PBS etc. is a pharmaceutically acceptable carrier.

Issekutz teaches the use of TA-2, an Ig Kappa antibody specific for VLA4 for inhibiting lymphocyte migration in vivo (see materials and methods and figure 1).

Elices teaches anti-VLA4 antibodies which inhibit ICAM interactions.

The product of the claims is anticipated by the anti-VLA4 antibodies of the prior art.

The rejection is met by canceling claim 20.

CONCLUSION

Amendments and cancellations of the claims are to expedite prosecution and should not be construed as acquiescence to or agreement with the Examiner's rejections. Applicant reserves the option to further prosecute the same or similar claims in the present or in another patent application.

In view of the above, Applicant submits that the claims are in condition for allowance and requests such action. Please apply any charges not covered, or any credits, to Deposit Account 12-0080.

Respectfully submitted,

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